



PATENT
8012-1317

IN THE U.S. PATENT AND TRADEMARK OFFICE

In re application of

Satoshi OMURA et al.

Conf. 5881

Application No. 10/532,662

Group 1654

Filed January 19, 2006

Examiner H. Young

NOVEL SUBSTANCE FKI-1033 AND PROCESS
FOR PRODUCING THE SAME

DECLARATION UNDER RULE 132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Kazuro SIOMI, PhD, am employed in the Department of Drug Discovery Sciences of the current assignee, The Kitasato Institute for Life Sciences, Tokyo, Japan.

I have been engaged in researching compounds having ryanodine binding inhibition activity and arthropodocidal activity as a professor at the Laboratory of Biological Functions in the Department of Drug Discovery Sciences of Kitasato Institute for Life Sciences.

I am one of the inventors of the above-identified U.S. patent application. I am familiar with the Examiner's position that the recited FKI-1033 substance would have been anticipated under 35 USC §102(a) because WO 01/62268 A1 and WO 02/00202 A1 broadly disclose a generic structure which includes the recited FKI-1033 substance structure.

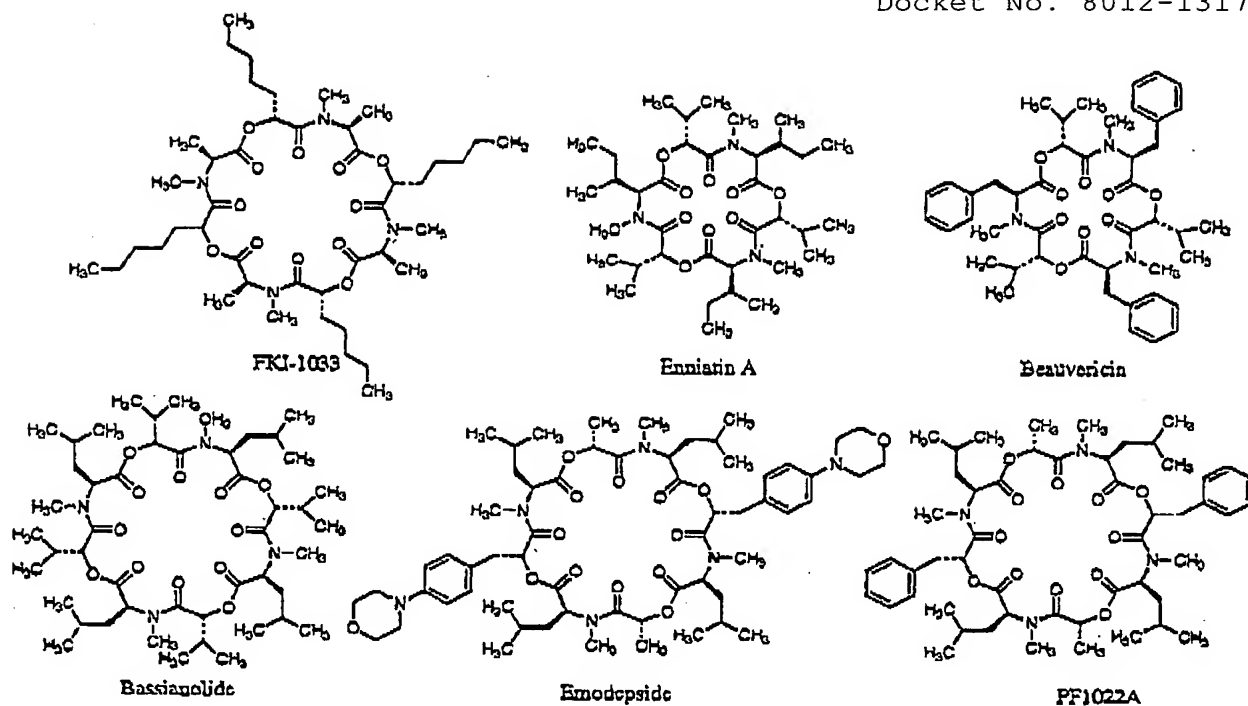
I have performed experiments to show that the compound of the present invention has superior ryanodine

binding inhibition activity and arthropodicidal activity compared to known compounds suggested by the references.

1. Activity of the substance FKI-1033 against arthropods

KALBE et al. (2001, WO 01/62268 A1; 2002, WO 02/00202 A1) showed that the 24-ring membered cyclic depsipeptides have good endoparasitocidal activities. However, they did not mention their ectoparasitocidal (arthropodicidal) activities. Although insecticidal activity of cyclic depsipeptides has been reported in some papers, the substance FKI-1033 has special unexpected activity as shown below.

We compared the toxicity of the substance FKI-1033 and the other 24-ring membered cyclic depsipeptide, emodepside against adult cattle ticks, *Boophilus microplus*. Emodepside is described in page 12, lines 9-10 of 2001, WO 01/62268 A1 as "particularly preferred" and page 12, lines 12-16 of 2002, WO 02/00202 A1 as "an especially preferred example". The substance FKI-1033 killed 100% of the ticks at 20 µg/ml in tick immersion test, while emodepside did not kill the ticks at 100 µg/ml. Moreover, the substance FKI-1033 killed 100% of the ticks at 0.16 µg in tick injection test, while emodepside killed 100% of the ticks at 20 µg. Therefore, the substance FKI-1033 is suggested to show very potent activity to some arthropods, which cannot be conceived easily.



2. Ryanodine binding inhibition activity of the substance FK1-1033

The substance FK1-1033 showed 50% ryanodine binding inhibition activity against American cockroach (*Periplaneta Americana*) ryanodine receptor at 4.2 μM , which has been described in WO 2004/044214. We studied the ryanodine binding inhibition activity of some other cyclic depsipeptides. All tested 24-ring membered cyclic depsipeptides (bassianolide and PF1022A) and 18-ring membered cyclic depsipeptides (enniatin A and beauvericin) showed no binding inhibition activity at 110 μM . PF1022A is described at page 11 of 2001, WO 01/62268 A1 and page 11 of 2002, WO 02/00202 A1 as "the compound PF 1022". Therefore, it is suggested that cyclic depsipeptides having ryanodine binding inhibition activity need to have some peculiar structure such as the substance FK1-1033.

Cyclic depsipeptides are composed of amino acids and hydroxy acids. The substance PKI-1033 is the first compound that has very small side chain at amino acids and very long straight side chain at hydroxy acids. This structure is suggested to affect its ryanodine binding inhibition activity and also its special arthropodicidal activity.

I further declare further that all statements made herein of their own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.


Kazuro SHIOMI

March 9, 2007
Date